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Radical Triggered Three-Component Coupling Reaction of Alkenylboronates, α-Halocarbonyl Compounds and Organolithium Reagents: The Inverse Ylid Mechanism

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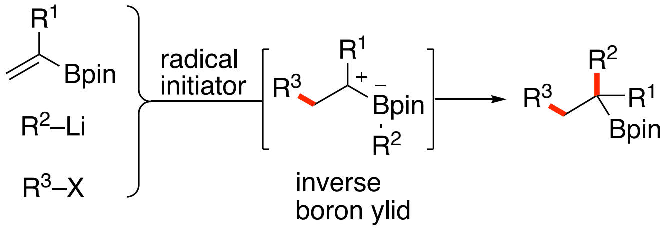
Abstract. An operationally simple protocol to affect a radical addition to alkenylboronates that spontaneously undergo a [1,2]-metalate shift is described. Overall, the reaction is a three-component coupling of an organolithium, alkenylboronic ester, and halide which takes place with broad scope and good to excellent yields. Experimental mechanistic investigations support the formation of a boron inverse ylid intermediate.



Introduction

Radical reactions have proven over the last decades to be a powerful tool in organic synthesis.[1-4] The intermolecular addition of carbon-centered radicals to alkenes is one of the mildest approaches for carbon–carbon bond formation.[5] Three component reactions involving either two consecutive radical reactions, or one radical reaction followed by an ionic reaction are currently attracting a lot of attention.[6-7] Our long-standing interest for radical reactions involving organoboron species prompted us recently to investigate the use of α-chloroalkylboronates in radical reactions and this led to the discovery of an intramolecular cyclopropanation reaction.[8-9] In these studies, the α -chloroalkylboronates were prepared according to Matteson's procedure, i.e. addition of the dichloromethyllithium to an alkylboronate. In order to find a different way to prepare α -haloalkylboronates, we decided to investigate the atom transfer mediated radical addition to alkenylboron derivatives. This approach was first investigated by Matteson who reported Kharasch type addition of radicals to vinylboronates.[10-11] Interestingly, Matteson discovered that the product of CCl_3Br radical addition to dibutyl vinylboronate afforded an α-arylated boronate upon treatment with aryl Grignard reagents such as 1-mesitylmagnesium bromide (Scheme 1, a).[12] The discovery of this now eponymous [1,2]-metalate rearrangement[13-14] opened a fruitful field of research as demonstrated by the work of Aggarwal,[15-18] Fu,[19] and Morken.[20-21] Recently, Zard reported a radical mediated xanthate transfer addition to MIDA-vinyl boronates and demonstrated the beneficial effect of complexing the Lewis acidic boron atom by a tertiary amino group (Scheme 1, b).[22] The complex formation speeds-up the addition of electrophilic radicals to the vinyl group. Moreover, it accelerates the xanthate transfer step since the radical adduct is no longer stabilized by a vacant p-orbital. These results strongly suggest that boronate complexes, that are negatively charged and are missing the empty p-orbital at boron should also act as efficient radical traps for halogen atom transfer processes. Based on this assumption, we decided to investigate the reactivity of alkenylboron ate complexes as radical trap in order to develop a three-component reaction involving a radical addition to a vinylboron ate complex followed by a halogen transfer and a final [1,2]-metalate rearrangement (Scheme 1, c). At an advanced stage of our study, Studer, [23-24] Aggarwal[25-26] and Morken[27] reported very closely related transformations. We report here a single-pot approach involving neither solvent switch nor the use of any additive (photoredox catalyst or co-solvent). Mechanistic evidence for the formation of an inverse ylid intermediate is provided.

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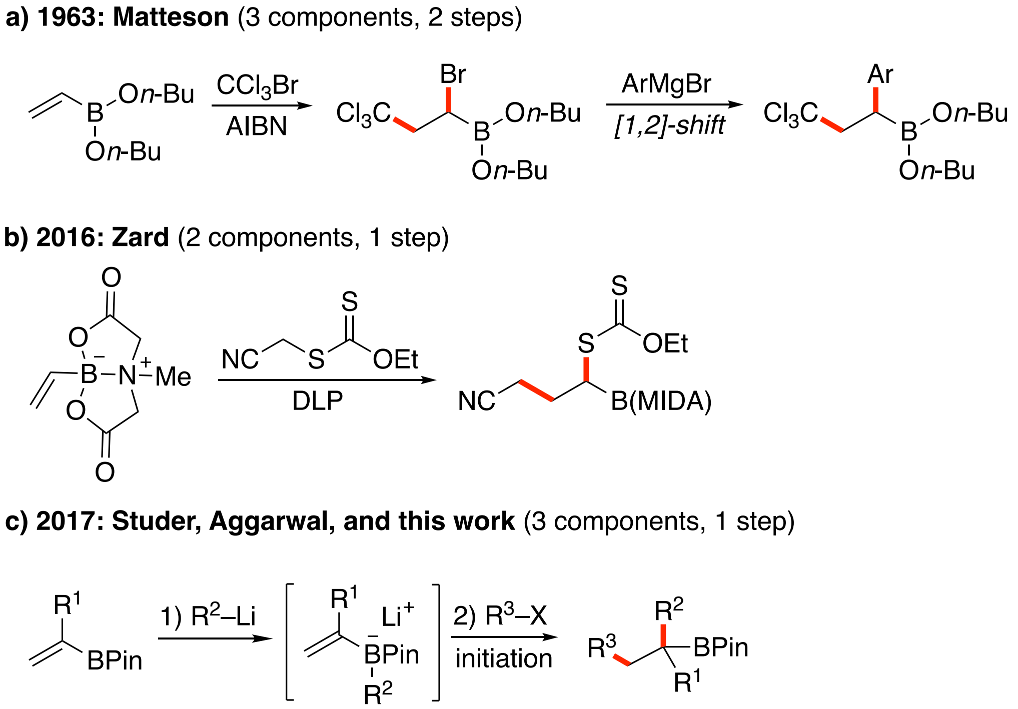


a) 1963: Matteson (3 components, 2 steps)

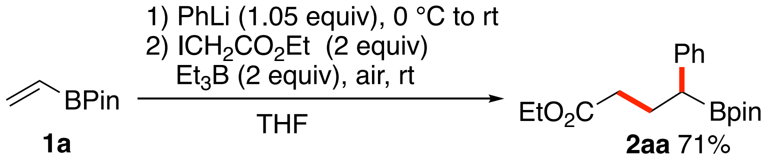
b) 2016: Zard (2 components, 1 step)

c) 2017: Studer, Aggarwal, and this work (3 components, 1 step)

Scheme 1. Radical mediated two and three component coupling processes involving vinylboronate.

Results and Discussion

Optimization and scope of the reaction. The coupling reaction between ethyl iodoacetate, vinylboronic acid pinacol ester **1a** (vinylBpin) and phenyllithium was attempted first by addition of PhLi (1.05 equiv) to a solution of the vinylBpin in THF at 0 °C. Ethyl iododoacetate (2 equiv) was added to the mixture at ambient temperature followed by Et_3B (2 equiv) and the reaction flask was open to air to initiate the radical process. Under these simple reaction conditions, the boronate **2aa** resulting from the desired three-component coupling reaction was obtained with an encouraging 71% yield (Scheme 2).

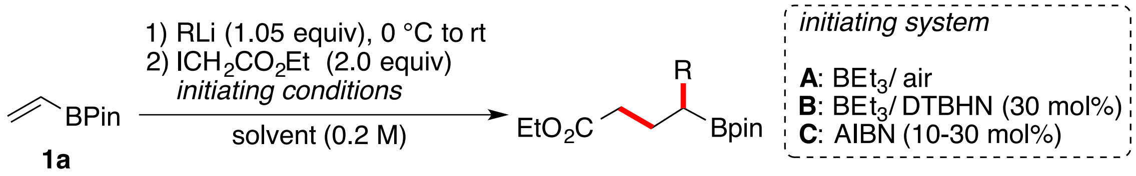


Scheme 2. Discovery of reaction.

The reaction was then extended to other organolithium derivatives (eq. 2, Table 1). The use of *n*-butyllithium afforded the boronate **4aa** in 75% yield under the same conditions (Table

1, entry 2). However, with secondary and tertiary alkyllithiums the boronates **6aa** and **7aa** were obtained in low yields (Table 1, entries 5,6). The used of di-*tert*-butylhyponitrite (DTBHN) at 60 °C increased the yield and the reproducibility (Table 1, entry 7). The lower yields observed with secondary and tertiary alkyllithiums relative to the primary ones suggest that a competing reaction is operating with the bulkier substrates. We hypothesized that the ethoxycarbonylmethyl radical was abstracting a hydrogen atom from tetrahydrofuran leading to the formation of HI by decomposition of the unstable 2-iodotetrahydrofuran. This process is leading to non-productive consumption of the starting iodoester and more importantly to decomposition of the vinylboron-ate complex by protonation. The fact that this competing reaction is more important for *t*-BuLi than for *n*-BuLi suggests that the *t*-BuLi·**1a** boronate complex is less reactive towards radicals than the *n*-BuLi·**1a** complex. This was experimentally confirmed by a competition experiment involving ethyl iodoacetate, vinylboronate **1a** (4.4 equivalents) and 2.2 equivalents of both *n*-BuLi and *t*-BuLi. The reaction afforded a 9:1 mixture of **5aa** and **7aa** in 40% yield (see supporting information).[28] A straightforward solution is to use a solvent with lower hydrogen atom donor properties.[29] Switching to the weakest possible hydrogen atom donor etheral solvent, i.e. *tert*-butyl methyl ether (TBME) gave enhanced results both with *n*-BuLi (Table 1, entry 3, 92% yield) and *t*-BuLi (Table 1, entry 8, 68% yield).[30] Testing the reaction with simply AIBN as the initiator and benzene as the solvent gave good results except in the case of *t*-BuLi complexes (Table 1, entries 4, 9).[31]

Table 1. Optimization of the initiation and the solvent for the one-pot three component coupling reaction between vinylBPin, ICH_2CO_2Et, and RLi species.



Entry	RLi	Product	Initiating system	Solvent	Temp.	Reaction time	Yield
1	PhLi	**2aa**	A	THF	25 °C	16 h	71%
2	*n*-BuLi	**4aa**	A	THF	25 °C	16 h	75%

3	*n*-BuLi	**4aa**	B	TBME	60 °C	1.5 h	92%
4	*n*-BuLi	**4aa**	C	benzene	85 °C	2 h	78%
5	*s*-BuLi	**6aa**	A	THF	25 °C	16 h	17%
6	*t*-BuLi	**7aa**	A	THF	25 °C	16 h	21%
7	*t*-BuLi	**7aa**	B	THF	60 °C	1.5 h	44%
8	*t*-BuLi	**7aa**	B	TBME	60 °C	1.5 h	68%
9	*t*-BuLi	**7aa**	C	benzene	85 °C	2 h	23%

The reaction conditions optimized above (conditions B in TBME) have been tested with vinylboronic and 2-propenylboronic acid pinacol esters **1a** and **1b**, different halides (usually iodides) and organolithium reagents. The results are summarized in Scheme 3. The reaction of iodoacetonitrile with PhLi·**1a** afforded the desired nitrile **2ac** in only 33% yield. Performing the reaction at room temperature (air initiation) dramatically improved the yield to 76%. Remarkably, the reaction of diethyl 2-bromo-2-methylmalonate with PhLi·**1a** worked fine and afforded the diester **2ad** in 68% yield.[32] The vinylboronate derived from (+)-pinanediol afforded **4ca** as 1:1 mixture of diastereomers. Reactions involving secondary and tertiary organolithium were then investigated. Pleasingly, our method works fine with these stubborn couplings reactions. Reactions involving *s*-BuLi and *i*-PrLi and ethyl iodoacetate provided the coupling products in 52–85% yield. Similarly, the reaction of PhSO$_2$CH$_2$I and EtO$_2$CCH$_2$I with *t*-BuLi·**1a** and *t*-BuLi·**1b** afforded **7aa**, **7ba** and **7ab** in 62–69% yield.[33] Careful product analysis of the coupling leading to **7aa** showed the presence of the more polar borinic ester **8** (7%) which was isolated and characterized. Such a borinic ester has been identified in the homologation of a bulky tertiary boronic ester with chloromethyllithium.[34] The reaction with iodoacetonitrile gave a low yield with the vinylboronate **1a** (**7ac**, 24%) but a satisfactory yield was obtained with the more reactive isopropenylBpin **1b** (54% for **7bc)**.[35] As can be generally seen in all the examples, and especially when comparing **7ac** to **7bc**, the methyl group increases the radical trap ability of the boronate complex. This effect was experimentally confirmed by a competition experiment involving a 1:1 mixture of **1a**/**1b** (excess), *n*-BuLi and EtO$_2$CCH$_2$I that gave **4aa**/**4ba** as 1:1.5 mixture (see supporting information).[36]

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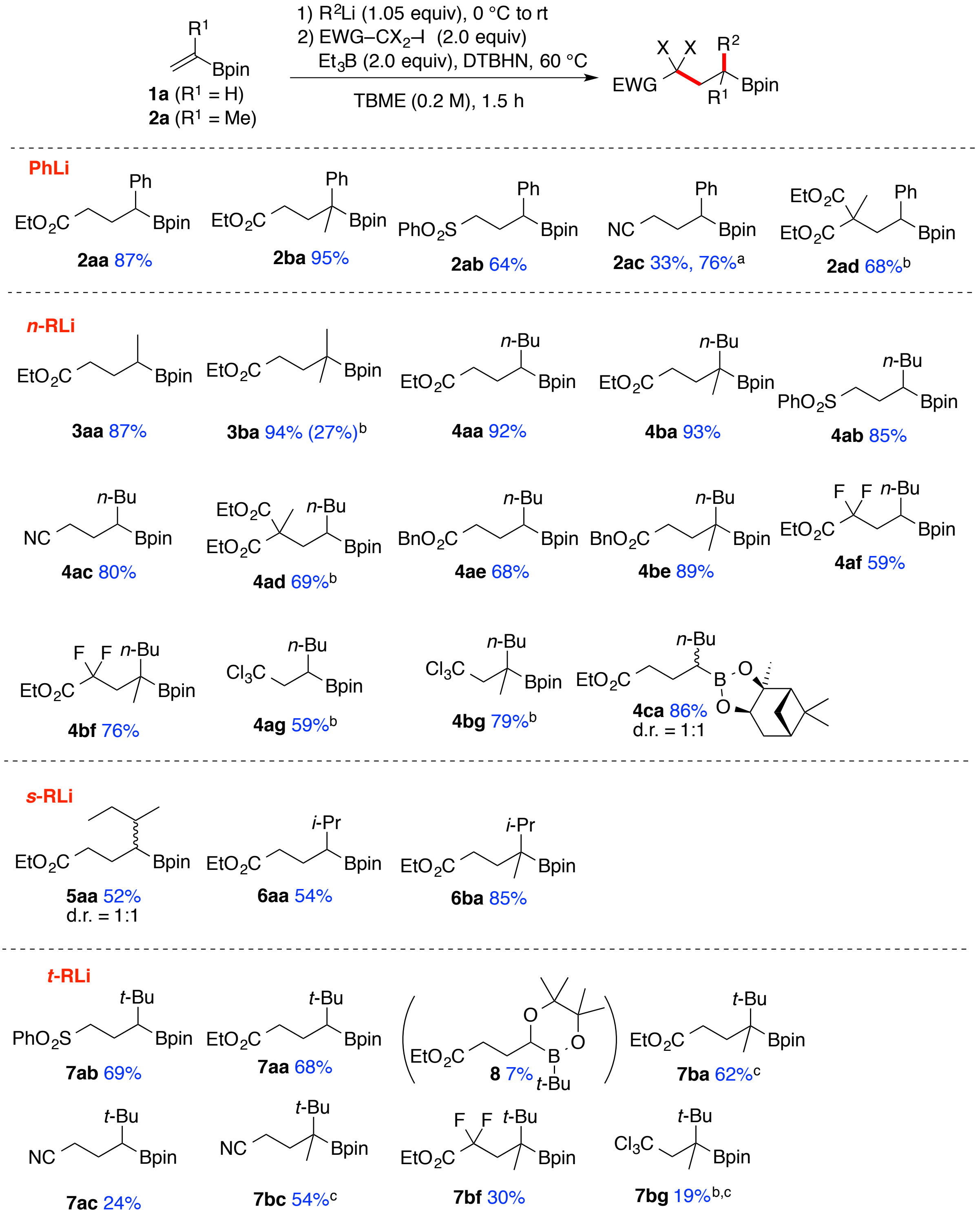
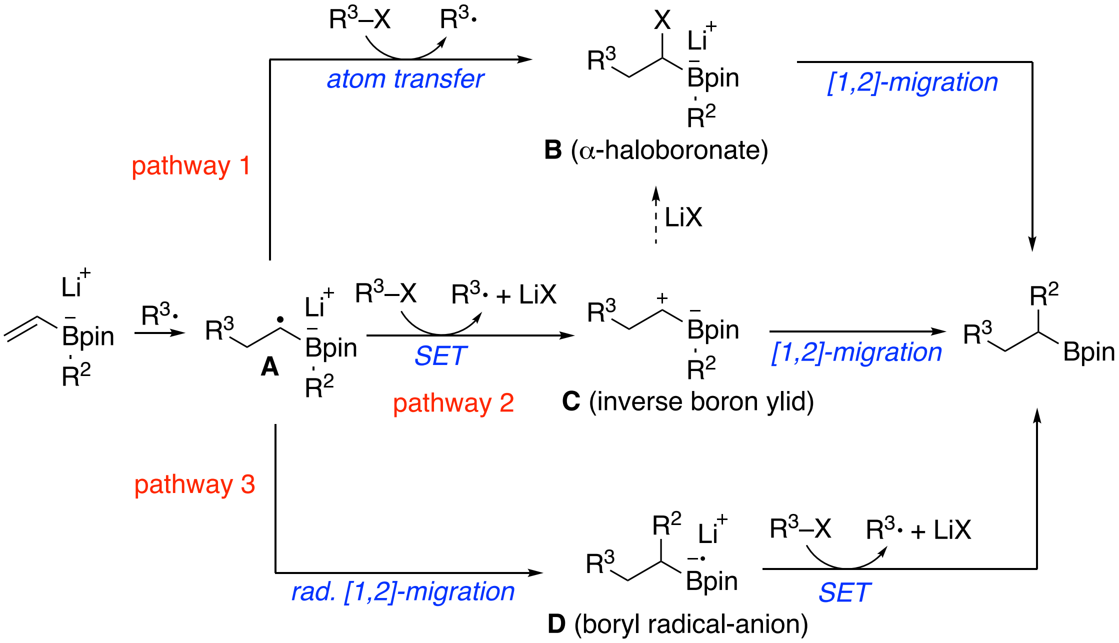


Scheme 3. Scope of the three-component coupling reaction. Reactions were performed on a 1.0 mmol scale and all yields reported are isolated after silica gel chromatography. a) Initiated with air at 25 °C; b) starting from the corresponding bromide; c) boronate complex prepared at –78 °C to avoid allylic deprotonation.

Mechanistic investigations. The three-component coupling process may follow different (competing) pathways as summarized in Scheme 4. Pathway 1 involves an atom transfer radical addition reaction leading to an α-haloboronate **B** that undergoes the classical [1,2]-metalate rearrangement. In pathway 2, the radical anion **A** can reduce the starting halide via a single electron transfer (SET) process that leads to an inverse ylid **C** which subsequently undergoes a fast migration reaction. Recombination of **C** with the halide anion would provide **B** and cannot be excluded, but is highly unlikely (intermolecular process vs. intramolecular 1,2-shift, low iodide concentration). Alternatively, in pathway 3, **A** could undergo a [1,2]-alkyl- or aryl-migration[37][38-39] leading to a boryl radical-anion **D** which could then propagate the chain via a reductive SET. Indeed, boryl radical anions such as $BH_3^{\bullet-}$ and $BH_2CN^{\bullet-}$ are known to abstract efficiently iodine atom presumably via a SET process.[40]

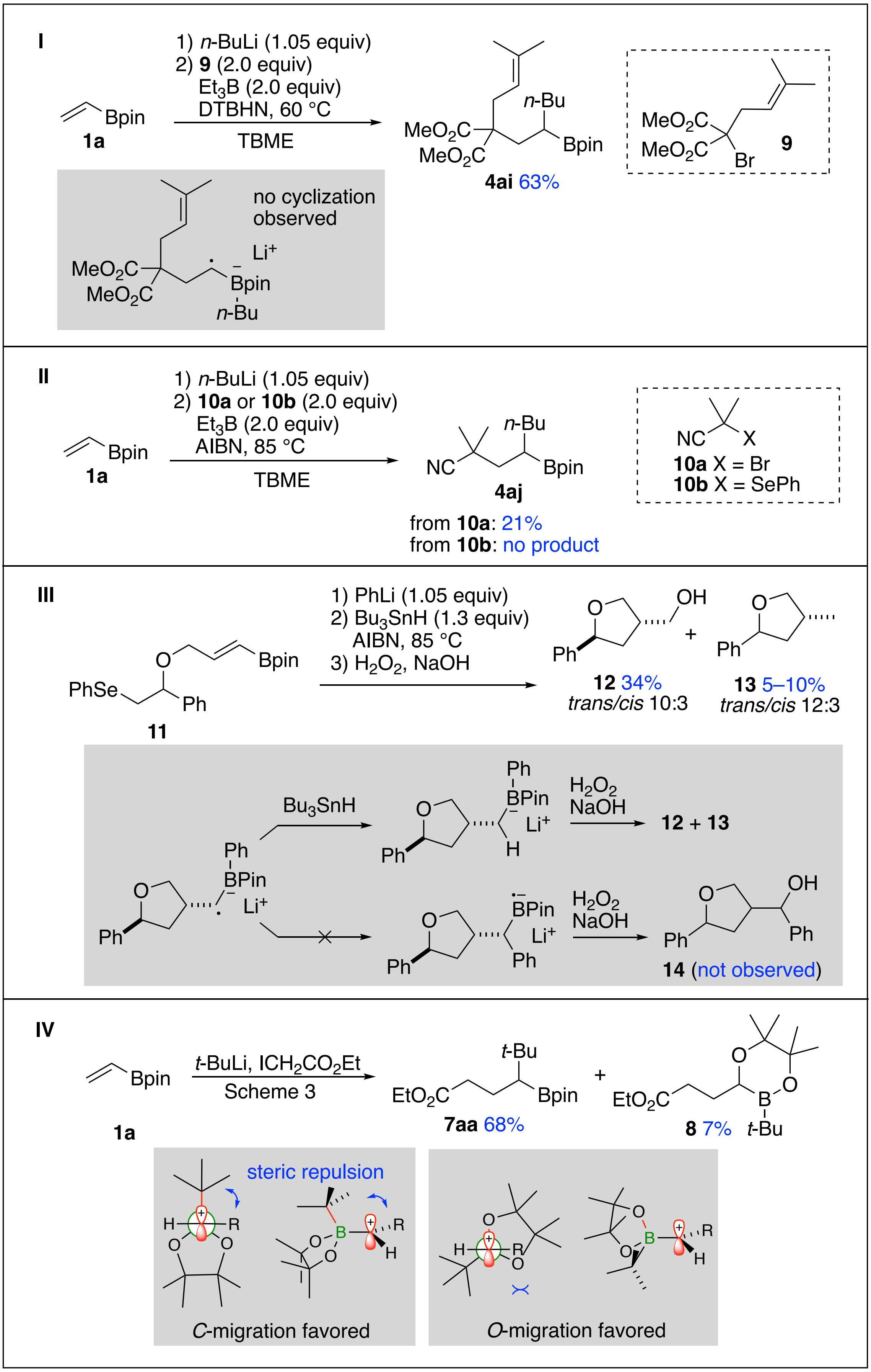


Scheme 4. Three possible mechanisms.

In order to gain more insight into the mechanism, a radical clock experiment with the 3,3-(dimethylprop-2-en-1yl)malonate **9** was used to probe the lifetime of the radical intermediate **A**. This reagent has been used recently for efficient radical annulations.[41-43] The reaction between **1a**, *n*-BuLi, and bromomalonate **9** afforded exclusively the product of

[1,2]-metalate rearrangement in 63% yield (Scheme 5, **I**). No product resulting from a radical cyclization process could be detected. Since the 5-*exo*-trig cyclization of the intermediate hexenyl radical is expected to be very fast, this result supports the SET mechanism (Scheme 4, pathway 2 or 3). Indeed, the rate constant for the radical cyclization can be estimated to be around 10^7 s^{-1} at room temperature[44] and the rate constant for the atom transfer step involving a primary alkyl radical and diethyl 2-bromo-2-methylmalonate has been reported to be 0.75–1.3 × 10^6 M^{-1} s^{-1} at 50 °C.[45] Under our reaction conditions ([**9**] ≤ 0.4 M), the bromine atom transfer process is not expected to compete with the cyclization process. The second experiment supporting pathway 2 was the coupling of **1a**, *n*-BuLi and either the bromide **10a** or the selenide **10b** (Scheme 5, **II**). The bromide **10a** afforded the product **4aj** in 18% yield whereas neither **4aj** nor a product derived from a PhSe group transfer process was obtained from the reaction of **1a** with **10b** and the starting selenoacetate was not fully consumed. The lack of product resulting from SePh transfer process and low conversion speaks against the atom transfer pathway 1. A reaction via pathway 3 should have been working with both substrates since the rate transfer of bromine atoms and SePh groups are very close.[46] However, the reduction potentials of these two substrates are very different. A bromide being much easier to reduce than a selenide explains why **10b** cannot efficiently react via a SET mechanism. Then, an experiment was designed to probe the feasibility of a radical 1,2-migration with R^2 = phenyl group to maximize the chance to observe a radical 1,2-migration (neophyl type rearrangement).[47-48] For this purpose, the selenide **11** was converted to its ate complex by addition of PhLi and treated with Bu_3SnH and AIBN (Scheme 5, **III**). Using PhLi resulted in no radical coupling products. However with the use of *n*-BuLi, and under these reductive conditions, tetrahydrofurans **12** and **13** resulting from a 5-*exo*-trig cyclization followed by reduction of the α-boronate radical were the only isolated products. Protonolysis of the cyclized ate complex was expected to be unselective leading, after oxidative work-up, to **12** and **13**. No product arising from a [1,2]-migration such as **14** could be observed. Finally, the formation of the borinate byproduct **8** during the coupling involving **1a**, *t*-BuLi and Et_2OCH_2I is compatible with the inverse ylid pathway 2 but not with the radical 1,2-migration proposed in pathway 3. A concerted SET–[1,2]-migration mechanism cannot be completely ruled out at the moment. However, the isolation of the *O*-migration product **8** in the reaction involving the bulky *tert*-butyllithium (Scheme 5, **IV**) tends to support the formation of an inverse ylid intermediate followed by a fast [1,2]-shift.

Indeed, the borinate **8** is much less stable than the boronate **7aa** (a B–O bond is much stronger than a B–C bond). In a concerted mechanism, the migrating B–C respectively the B–O bonds should be already partly cleaved in the transition state. Therefore, *C*-migration is expected to be highly favored. On the other hand, the chemoselectivtiy of the [1,2]-migration of the inverse ylid is expected to be controlled by its conformation. The presence of a bulky *tert*-butyl group at boron destabilizes the major conformation leading to *C*-migration making the minor conformation leading to *O*-migration competitive. Similar effects have been observed in the case of 1-chloro- and 1-bromoalkylboronate complex, the more polarized 1-chloro derivative favoring the *O*-migration compared to the 1-bromoderivative.[34] Based on these results, a mechanism involving an electron transfer process leading to the formation of an inverse boron ylid of type **C** that undergoes a fast rearrangement is privileged (pathway 2). Both Studer[23] and Aggarwal[25] proposed a similar mechanism for their reactions but the electron transfer process could only be experimentally demonstrated when the strongly oxidizing Togni's reagent was used to generate a trifluoromethyl radical.[23]


I
1) n-BuLi (1.05 equiv)
2) 9 (2.0 equiv)
Et3B (2.0 equiv)
DTBHN, 60 °C
TBME
Bpin
1a
MeO2C
MeO2C
n-Bu
Bpin
4ai 63%
MeO2C
MeO2C
Br
9
no cyclization observed
Li+
Bpin
n-Bu
II
1) n-BuLi (1.05 equiv)
2) 10a or 10b (2.0 equiv)
Et3B (2.0 equiv)
AIBN, 85 °C
TBME
Bpin
1a
NC
n-Bu
Bpin
4aj
from 10a: 21%
from 10b: no product
NC
X
10a X = Br
10b X = SePh
III
1) PhLi (1.05 equiv)
2) Bu3SnH (1.3 equiv)
AIBN, 85 °C
3) H2O2, NaOH
O
Bpin
PhSe
Ph
11
O
OH
Ph
+
12 34%
trans/cis 10:3
O
Ph
13 5–10%
trans/cis 12:3
Bu3SnH
Ph
BPin
Li+
O
Ph
H
H2O2
NaOH
12 + 13
BPin
Li+
Ph
OH
14 (not observed)
IV
Bpin
1a
t-BuLi, ICH2CO2Et
Scheme 3
EtO2C
t-Bu
Bpin
7aa 68%
+
EtO2C
O
O
B
t-Bu
8 7%
steric repulsion
H
R
O
B
C-migration favored
O-migration favored

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Scheme 5. Mechanistic investigations.

Conclusions

We have developed an experimentally simple procedure to couple an alkyl iodide (or bromide) activated by an electron withdrawing group to a alkenylboronic ester and an organolithium species. The reaction affords functionalized α-branched alkylboronate esters in good to excellent yield. This procedure does not require the use of a catalyst and it can be performed in a one pot-process without solvent switch. Strong evidence for the formation of an inverse boron ylid intermediate is presented and provides an attractive foundation for future developments.

Experimental Section

General Procedure (DTBHN initiation)

To a solution of the vinyl or isopropenyl boronic acid pinacol ester (1.00 mmol) in TBME (5 mL) at 0 °C was added dropwise a solution of organolithium (1.05 mmol). After stirring for 30 min at 0 °C, the reaction mixture was allowed to warm to rt and to it were added BEt_3 solution (2.0 M in benzene, 1.0 mL, 2.0 mmol), the radical precursor (2.0 mmol), and DTBHN (52 mg, 0.30 mmol) in that order. The reaction mixture was heated to 60 °C, and gently refluxed for 1.5 h. The reaction was cooled to rt and partitioned between TBME (20 mL) and water (15 mL), acidified with 1.0 M aq. HCl (2–5 mL). The organic phase was washed once more with water (20 mL), and the combined aq. phases were extracted once with TBME (5-10 mL). The combined ethereal phases were washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). After drying over Na_2SO_4, the solution was filtered through a silica plug (i.d. = 20 mm; depth = 20–30 mm) protected with a cotton wad. The crude mixture was concentrated *in vacuo* and directly submitted to FC.

Coupling product 2ba

General procedure was followed and the crude was submitted to FC (gradient = 2–5% AcOEt/heptanes) to afford **2ba** (314 mg, 0.945 mmol, 95%) as a clear, viscous oil (R_f = 0.38 in AcOEt/heptanes 15:85). ^1H NMR (300 MHz, CD_2Cl_2): δ 7.34 – 7.22 (m, 4H), 7.19 – 7.07 (m, 1H), 4.03 (q, J = 7.1 Hz, 2H), 2.27 – 1.86 (m, 4H), 1.31 (s, 3H), 1.19 (m, 15H) [interpreted as

1.21 (br s, 6H), 1.22 (br s, 6H) + 1.19 (t, J = 7.1 Hz, 3H)]. ^{13}C NMR (75 MHz, CD_2Cl_2): δ 174.2 (C_q), 146.5(C_q), 128.5 (CH), 127.3 (CH), 125.7 (CH), 83.9 (C_q), 60.4 (CH_2), 34.6 (CH_2), 30.6 (CH_2), 24.8 (CH_3), 24.7 (CH_3), 21.1 (CH_3), 14.4 (CH_3). ^{11}B NMR (96 MHz, CD_2Cl_2): δ 33.9 (s). IR (thin film): ν = 1732 (s) cm^{-1}. HRMS (ESI): calculated for $C_{19}H_{29}BO_4Na$ $[M+Na]^+$: 355.2051; found: 355.2053.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords

boronic esters, radical reaction, single electron transfer, inverse boron ylid, Matteson rearrangement

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[28] A similar experiment involving PhLi and *n*-BuLi gave **2a**/**2b** as a1:1.2 mixture in 67% yield

[29] Probably for the same reason, Studer and Aggarwal are both using a solvent switch afer the formation of the ate complex to acetonitrile and 1,3-dimethyl-2-imidazolidinone, respectively.

[30] Benzene gave similar results but the more benign TBME was kept for the rest of our study.

[31] Studer and coworkers have also reported that, after a solvent switch from THF to acetonitrile, Et_3B (ref. 23) and light (ref. 24) were both efficiently initiating reactions involving α-iodoesters.

[32] Attempt to use diethyl bromomalonate was unsuccessful. This radical precursor was found to protonate the ate complex before the radical reaction could take place.

[33] For the reaction involving **1b**, the formation of the ate complex with *tert*-butyllithium had to be performed at –78 °C to avoid competing allylic deprotonation.

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[35] In this case, the competing formation of an azaboron enolate by reaction of the cyanomethyl radical with Et_3B cannot be excluded

[36] The presence of the methyl substitutent is also expected to enhance the reducing power of the radical anion intermediate and favor the SET recution of the iodide regenerating the starting radical.

[37] Radical 1,2-aryl shift (neophyl rearrangement) is well-documented in the literature.

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